Selective serotonin reuptake inhibitor prescribing before, during and after pregnancy

Charlton, R. A.; Jordan, S.; Pierini, A.; Garne, E.; Neville, A. J.; Hansen, A. V.; Gini, R.; Thayer, D.; Tingay, K.; Puccini, A.

Published in:
BJOG : An International Journal of Obstetrics and Gynaecology

DOI:
10.1111/1471-0528.13143

DOI: 10.1111/1471-0528.13143
www.bjog.org

Selective serotonin reuptake inhibitor prescribing before, during and after pregnancy: a population-based study in six European regions

RA Charlton,[a] S Jordan,[b] A Pierini,[c] E Garne,[d] AJ Neville,[e] AV Hansen,[d] R Gini,[f] D Thayer,[g] K Tingay,[g] A Puccini,[h] HJ Bos,[i] AM Nybo Andersen,[j] M Sinclair,[k] H Dolk,[l] LTW de Jong-van den Berg[i]

[a] Department of Pharmacy and Pharmacology, University of Bath, Bath, UK [b] Department of Nursing, College of Human and Health Sciences, Swansea University, Swansea, UK [c] Institute of Clinical Physiology – National Research Council (IFC-CNR), Pisa, Italy [d] Paediatric Department, Hospital Lillebaelt, Kolding, Denmark [e] IMER (Emilia Romagna Registry of Birth Defects), Azienda Ospedaliero-Universitaria di Ferrara, Ferrara, Italy [f] Agenzia Regionale di Sanità Della Toscana, Florence, Italy [g] Centre for Health Information, Research and Evaluation, Swansea University, Swansea, UK [h] Drug Policy Service, Emilia Romagna Region Health Authority, Bologna, Italy [i] Pharmacoepidemiology and Pharmacoeconomics Unit, Department of Pharmacy, University of Groningen, Groningen, the Netherlands [j] Department of Public Health, University of Copenhagen, Copenhagen, Denmark [k] Maternal, Fetal and Infant Research Centre, [l] Institute of Nursing, University of Ulster, Ulster, UK
Correspondence: Dr RA Charlton, Department of Pharmacy and Pharmacology, University of Bath, Bath BA2 7AY, UK.
Email r.a.charlton@bath.ac.uk

Accepted 8 September 2014. Published Online 28 October 2014.

Objective To explore the prescribing patterns of selective serotonin reuptake inhibitors (SSRIs) before, during and after pregnancy in six European population-based databases.

Design Descriptive drug utilisation study.

Setting Six electronic healthcare databases in Denmark, the Netherlands, Italy (Emilia Romagna/Tuscany), Wales and the rest of the UK.

Population All women with a pregnancy ending in a live or stillbirth starting and ending between 2004 and 2010.

Methods A common protocol was implemented across databases to identify SSRI prescriptions issued (UK) or dispensed (non-UK) in the year before, during or in the year following pregnancy.

Main outcome measures The percentage of deliveries in which the woman received an SSRI prescription in the year before, during or in the year following pregnancy. We also compared the choice of SSRIs and changes in prescribing over the study period.

Results In total, 721 632 women and 862 943 deliveries were identified. In the year preceding pregnancy, the prevalence of SSRI prescribing was highest in Wales [9.6%; 95% confidence interval (CI_{95}), 9.4–9.8%] and lowest in Emilia Romagna (3.3%; CI_{95}, 3.2–3.4%). During pregnancy, SSRI prescribing had dropped to between 1.2% (CI_{95}, 1.1–1.3%) in Emilia Romagna and 4.5% (CI_{95}, 4.3–4.6%) in Wales. The higher UK pre-pregnancy prescribing rates resulted in higher first trimester exposures. After pregnancy, SSRI prescribing increased most rapidly in the UK. Paroxetine was more commonly prescribed in the Netherlands and Italian regions than in Denmark and the UK.

Conclusions The higher SSRI prescribing rates in the UK, compared with other European regions, raise questions about differences in the prevalence and severity of depression and its management in pregnancy across Europe.

Keywords Drug utilisation, electronic health records, pregnancy, serotonin uptake inhibitors.

Please cite this paper as: Charlton RA, Jordan S, Pierini A, Garne E, Neville AJ, Hansen AV, Gini R, Thayer D, Tingay K, Puccini A, Bos HJ, Nybo Andersen AM, Sinclair M, Dolk H, de Jong-van den Berg LTW. Selective serotonin reuptake inhibitor prescribing before, during and after pregnancy: a population-based study in six European regions. BJOG 2015;122:1010–1020.

Introduction

Depression is common among women of childbearing age,[1] and the prevalence of depression affecting women during pregnancy has been reported to range from 6% to 13%.[2,3] Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed class of antidepressant,[4] and studies evaluating patterns of prescribing have shown that between

2.8%[5] and 10.2%[6] of women receive an SSRI prescription at some point during pregnancy. The proportion of pregnant women prescribed or dispensed with an SSRI varies by geographical location, study setting and calendar year, with an increase in prescribing over time observed between 1995 and 2008.[6–8]

The effect of *in utero* SSRI exposure and exposure via breast milk is incompletely understood; some, but not all, observational studies have indicated that exposure during pregnancy is associated with a number of adverse perinatal and fetal outcomes.[9–16] Untreated depression and treatment discontinuation, however, are not without potential risks to both the woman and the developing fetus.[15,17] Complex decisions therefore need to be made, by women and healthcare professionals, to balance the potential risks of fetal exposure with the risks of no treatment or treatment discontinuation. As many pregnancies are unplanned,[18] it is important that women of childbearing age receive appropriate information when SSRI treatment is commenced.

The extent of SSRI prescribing during pregnancy has been reported for some geographical regions, but for others it is still unknown. To our knowledge, this is the first study including pre- and post-pregnancy prescribing in multiple areas of Europe. An understanding of variations in prescribing patterns can inform the interpretation of potential safety signals and identify areas requiring further research. This study aims to describe the extent and nature of SSRI prescribing to women before, during and after pregnancy in six European population-based healthcare databases between 2004 and 2010.

This study forms part of EUROmediCAT,[19] a Seventh Framework Programme study funded by the European Union that aims to make more systematic use of electronic healthcare databases in combination with EUROCAT[20] congenital anomalies data.

Methods

Setting

Six population-based electronic healthcare databases, which captured pregnancies and prescription data, contributed to the study: two in Italy (Tuscany[21] and Emilia Romagna[22]), two in the UK [the Secure Anonymised Information Linkage (SAIL) Databank in Wales[23,24] and the UK-wide Clinical Practice Research Datalink (CPRD)[25] with data from Wales excluded], one in Denmark[26–28] and one in the Netherlands[29] (Table 1). A more detailed description of the databases can be found elsewhere.[30] Where multiple databases were linked, such as in Denmark where the information on all pregnancies from the Danish National Patient Register was linked to the Danish National Prescription Registry, for the remainder of this paper these linked databases are referred to as a single database. Ethical and data access approvals were obtained for each database from the relevant governance infrastructures.

Data extraction

All databases followed a common protocol. Within each database, all pregnancies starting and ending between 1 January 2004 and 31 December 2010 (except for Denmark, where the final date was 31 December 2009) were identified and the best estimate of the start of pregnancy was calculated. Pregnancies were eligible for the study if they ended in a delivery (live birth or stillbirth) and the woman had been present in the database, capturing prescription data, during the entire year before pregnancy, throughout pregnancy and during the entire year following pregnancy. All SSRI prescriptions recorded in the databases during the time period of interest were identified. In the UK databases, this included all SSRI prescriptions issued, whereas, in the other databases, it included only SSRI prescriptions actually dispensed. SSRIs were defined as products with an Anatomical Therapeutic Chemical (ATC) code starting with N06AB and included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine and escitalopram.

Analyses

The percentage of women receiving (issued/dispensed) an SSRI prescription in each of the databases was calculated for the year leading up to pregnancy, during pregnancy and for the year following pregnancy. Percentages were calculated by dividing the number of deliveries in which the woman received an SSRI prescription during the period of interest by the total number of deliveries. Prescribing patterns were described for each pregnancy trimester and for 3-month time periods during the years before and after pregnancy. The choice of specific SSRI, co-prescribing of antipsychotics, anxiolytics and hypnotics, and changes in prescribing over calendar time were described and compared.

Results

In the six databases, 721 632 eligible women with 862 943 deliveries were identified. The mean maternal age at the start of pregnancy ranged from 27.7 years [standard deviation (SD), 6.1] in Wales to 32.3 years (SD, 4.9) in Italy (Emilia Romagna), and was significantly lower in Wales than in other regions, including the rest of the UK (CPRD)] ($P < 0.001$). Of all the deliveries, 5.4% [95% confidence interval (CI_{95}), 5.3–5.4%] of women received a prescription for an SSRI during the year before pregnancy, ranging from 3.3% (CI_{95}, 3.2–3.4%) in Emilia Romagna to 9.6% (CI_{95}, 9.4–9.8%) in Wales. During pregnancy, the percentage of women receiving an SSRI prescription fell to 2.3% (CI_{95}, 2.2–2.3%), ranging from 1.2% (CI_{95}, 1.1–1.3%)

Table 1. Overview of databases contributing to the study

	Country/region					
	Netherlands	**Denmark**	**Italy: Emilia Romagna**	**Italy: Tuscany**	**UK***	**Wales**
Involves database record linkage	No	Yes	Yes	Yes	No	Yes**
Coverage	Regional	National	Regional	Regional	Approximately 8.5% of UK population	Approximately 40% of GP practices
Population base	~500 000	~5 000 000	~4 200 000	~3 700 000	~5 000 000***	~2 000 000
Database for live and stillbirth pregnancy identification	IADB.nl	Danish National Patient Registry	Certificate of Delivery Assistance (CeDAP)	Certificate of Delivery Assistance (CeDAP) Hospital Discharges Registry	Clinical Practice Research Datalink (CPRD)****	National Community Child Health Database (NCCHD)
Database for medicine use data	IADB.nl	Danish National Prescription Registry	Emilia-Romagna Prescription Database (ERPD)	Tuscany Prescription Database	Clinical Practice Research Datalink (CPRD)	The General Practice (GP) Dataset
Source for medicine use data	Pharmacy dispensing	Pharmacy dispensing	Pharmacy dispensing*****	Pharmacy dispensing and Healthcare Facilities Dispensing*****	GP practice prescribing	GP practice prescribing
Capture GP prescribing	Yes	Yes	Yes	Yes	Yes	Yes
Capture outpatient prescribing	Yes	Yes	Yes*****	Yes*****	Yes******	Yes******
Capture inpatient prescribing	No	No	No	No	Some	Some
Date of last menstrual period recorded	Estimated for all	Calculated from gestational age	Calculated from gestational age	Calculated from gestational age	Yes for 40% Estimated for 60%	Yes for 80% Estimated for 20%
Smoking status	No	Yes*******	Yes	Yes	Yes	Some
Alcohol consumption	No	No	No	No	Yes	Some
Pre-pregnancy body mass index	No	Yes*******	No	Yes	Yes	Some
A measure of socioeconomic status	Yes	Yes	Yes	Yes	Yes	Yes

*Excluding practices in Wales to avoid duplication of pregnancies in the database contributing data for Wales.
**Secure Anonymised Information Linkage (SAIL) Databank.
***The size of the population captured by the CPRD has grown steadily over time and was approximately 5.0 million in May 2012.
****Previously the General Practice Research Database (GPRD).
*****Only products reimbursed by the Italian National Health Service and excluding those dispensed to outpatients in a hospital pharmacy.
******Excluding prescriptions initiated by a specialist in a hospital outpatient department, but any repeat prescriptions subsequently issued by the GP were captured.
*******Available for pregnancies that result in a delivery, but not for those that end in a pregnancy loss.

in Emilia Romagna to 4.5% (CI_{95}, 4.3–4.6%) in Wales (Table 2).

SSRI prescribing during the year before and after pregnancy was considerably higher in both of the UK databases compared with the Danish, Dutch and Italian databases (Table 2). The higher pre-pregnancy rates in the UK resulted in higher first trimester exposures. During the second and third trimesters however, where SSRI prescribing in all databases was at its lowest, the UK figures were in line with those of Denmark and the Netherlands (Figure 1). After pregnancy, SSRI prescribing increased more rapidly in the UK databases than in the others, and the prevalence of use was considerably higher than that pre-pregnancy. Outside the UK, by 6 months post-pregnancy, the prevalence of SSRI prescribing had returned to pre-pregnancy levels (Figure 1).

Figure 2 shows the starting and stopping prescribing scenarios for women who received an SSRI prescription during the year before pregnancy. Approximately 27% in the Dutch and Danish databases continued to receive prescriptions throughout pregnancy and during the year following pregnancy, compared with 10–12% in the UK databases and 4–9% in the Italian databases (Figure 2). Approximately 40% of women in the Dutch, Danish and UK databases stopped SSRI treatment before pregnancy and did not receive an SSRI prescription during pregnancy or in the year following delivery; in Italy, this percentage was higher at 56% in Tuscany and 67% in Emilia Romagna (Figure 2). In the UK databases, a further 25% discontinued before pregnancy, but restarted during the year after pregnancy; outside the UK, this scenario ranged from 10.8% to 14.6% of women. Women who discontinued SSRI use before pregnancy were quicker to restart following delivery in the UK and the Netherlands than in Italy and Denmark, with around 45% and 30% of the restarters, respectively, doing so within 3 months of delivery (data not shown). Overall, 0.5% (CI_{95}, 0.5–0.6%) of women received their first SSRI prescription during pregnancy, having not received a prescription during the year before pregnancy, ranging from 0.3% (CI_{95}, 0.2–0.4%) in the Netherlands to 1.0% (CI_{95}, 0.9–1.1%) in Wales (data not shown).

Between 2004 and 2009, a steady increase was observed in the percentage of deliveries in which the woman received a prescription for an SSRI during any of the pregnancy trimesters in Denmark, whereas smaller increases were observed in the UK databases (Figure 3). Fluoxetine and citalopram were the SSRIs of choice during pregnancy in Denmark and the UK databases, whereas, in Italy and the Netherlands, paroxetine was more popular (Figure 4). There was a steady increase in the use of citalopram and sertraline in the UK and Denmark during the study period and a slight decline in paroxetine (data not shown). All other prescribing remained relatively constant over time.

Levels of co-prescribing of products that act on the central nervous system were found to be higher in the Dutch database than in those of the UK and Denmark, particularly for anxiolytics (Supporting Information Figure S1). In the Danish and UK databases, levels of co-prescribing of anxiolytics and hypnotics/sedatives were similar pre- and post-pregnancy (between 4% and 6% of those receiving a prescription for an SSRI) with a small decline during the three pregnancy trimesters. Data on the co-prescribing of antipsychotics in Italy are likely to have underestimated

Table 2. Percentage of deliveries in the period 2004–2010 in which the woman received a prescription for a selective serotonin reuptake inhibitor (SSRI) in the year before pregnancy, during pregnancy or in the year following pregnancy

Country/region	Number of eligible deliveries in entire cohort	Mean maternal age at pregnancy start for entire cohort	SSRI prescription during:					
			The year before pregnancy		Any of the pregnancy trimesters		The year following pregnancy	
	n	Years (SD*)	%	95% CI	%	95% CI	%	95% CI
The Netherlands	13 935	29.4 (4.8)	3.9	3.6–4.2	2.3	2.0–2.5	4.3	4.0–4.6
Denmark**	320 846	30.0 (4.9)	4.1	4.0–4.1	2.3	2.3–2.4	4.1	4.0–4.2
Italy: Emilia Romagna	129 220	32.3 (4.9)	3.3	3.2–3.4	1.2	1.1–1.3	2.5	2.4–2.6
Italy: Tuscany	157 916	31.8 (4.9)	4.4	4.3–4.5	1.6	1.5–1.7	3.4	3.3–3.5
UK***	182 920	30.2 (6.1)	8.8	8.6–8.9	3.7	3.6–3.8	12.9	12.7–13.0
Wales	58 106	27.7 (6.1)	9.6	9.4–9.8	4.5	4.3–4.6	15.0	14.7–15.3

*Standard deviation.
**2004–2009.
***Excluding Wales to avoid duplication of pregnancies in the Secure Anonymised Information Linkage (SAIL) databank.

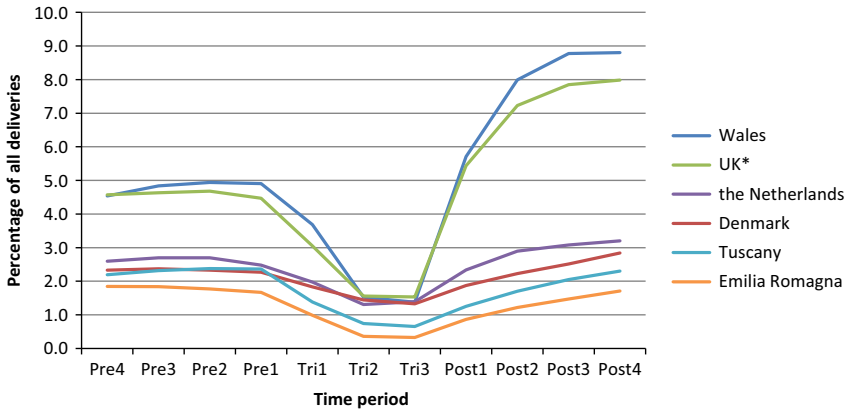

Figure 1. Percentage of all deliveries between 2004 and 2010 in which the woman received a prescription for a selective serotonin reuptake inhibitor (SSRI) during one or more of the time periods of interest. *Excluding Wales.

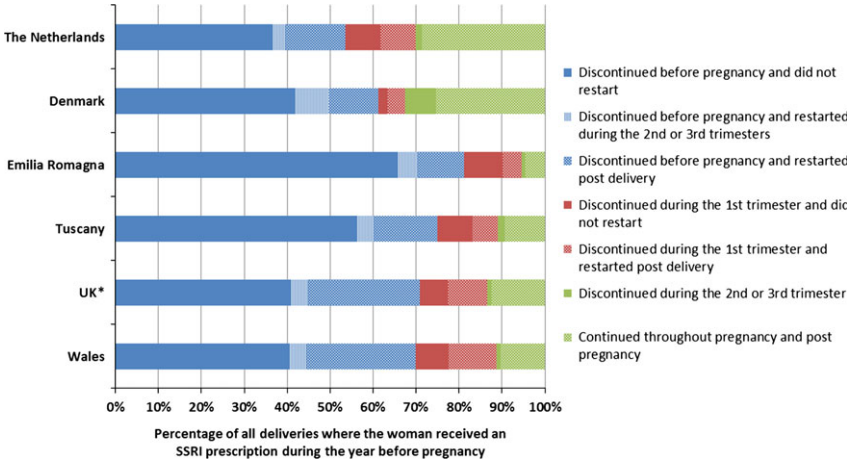

Figure 2. Starting and stopping scenarios for deliveries in which the mother had a selective serotonin reuptake inhibitor (SSRI) prescription during the year before pregnancy.

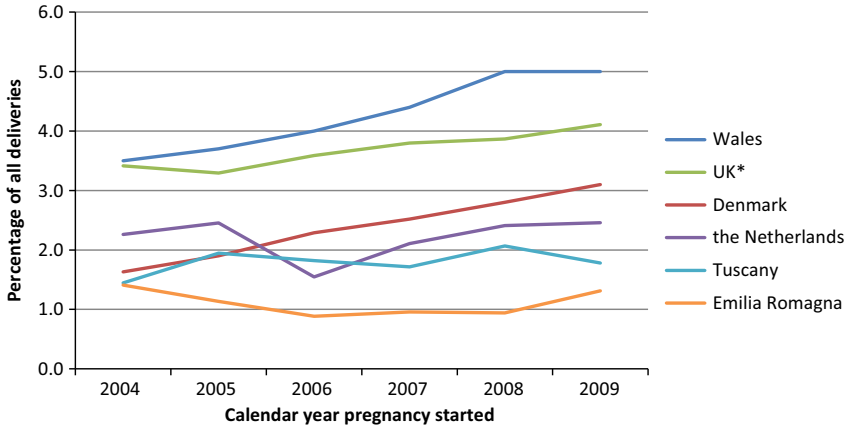

Figure 3. Percentage of deliveries in which the woman had a prescription for a selective serotonin reuptake inhibitor (SSRI) during any of the pregnancy trimesters by calendar year. *Excluding Wales.

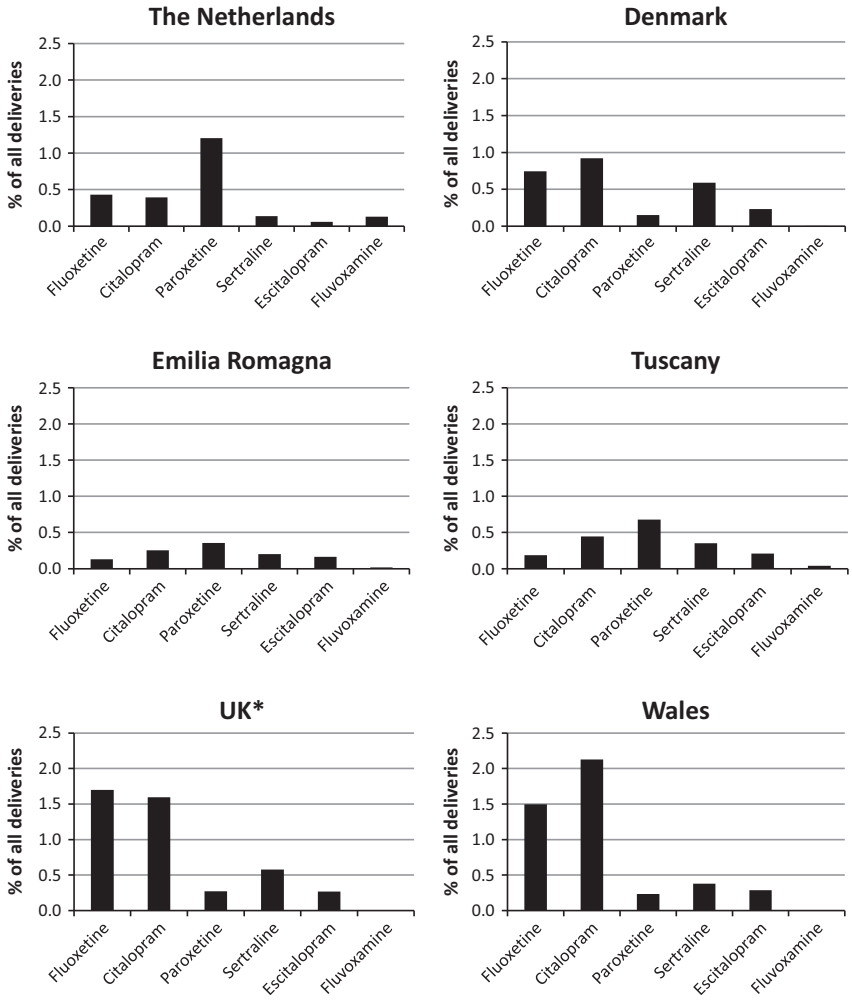

Figure 4. Percentage of all deliveries between 2004 and 2010 in which the woman received a prescription for the individual selective serotonin reuptake inhibitor (SSRI) during any of the pregnancy trimesters. *Excluding Wales.

actual use, as some of the products available are not reimbursed by the Italian health service and therefore escape recording. No data were available on the co-prescribing of anxiolytics and hypnotics/sedatives in Italy as these drugs are not reimbursed by the Italian health service.

Discussion

Main findings

Across Europe, marked differences appear to exist in the extent of SSRI prescribing to women before, during and after pregnancy, although these differences may be magnified by the UK databases recording prescriptions issued and the non-UK databases recording prescriptions dispensed. The prescribing of SSRIs was considerably higher in both UK databases than in the Danish, Dutch and Italian databases. In all databases, SSRI prescribing was at its lowest during the second and third trimesters of pregnancy. At least 40% of those with a prescription during the year preceding pregnancy discontinued before pregnancy and did not restart during the year following delivery. Of those who received a prescription in the year before pregnancy, the Danish and Dutch databases had the highest percentage of women continuing SSRI treatment throughout pregnancy and following delivery, and the Italian databases had the lowest. Differences were observed in terms of the most commonly prescribed SSRIs during pregnancy.

Strengths and limitations

This study captured over 850 000 pregnancies in six different areas of Europe. SSRI prescribing was recorded independently by the prescriber or pharmacist, and so ascertainment was not reliant on maternal involvement, which can result in potential recall and selection biases.[31,32] The shared data extraction protocol ensured that the study results were as comparable as possible across databases.

However, differences did exist between healthcare systems and the type of data available for research. Data in the UK databases were based on prescriptions issued, whereas, in Denmark, the Netherlands and Italy, data were based on prescriptions dispensed by a pharmacist. Some women who receive prescriptions for antidepressants choose not to redeem them from the pharmacist[33] and this may explain some, but not all, of the difference between the UK databases and other regions. The rate of prescription redemption is difficult to quantify and likely to vary by region, study population, type of drug and even a life event such as pregnancy. A study carried out in the UK in the late 1980s, looking at prescription redemption for all medicines,[34] found young women to be particularly poor redeemers, with 27.6% of women aged 16–29 years not redeeming their prescriptions; it is unclear whether this is still the case and whether it applies specifically to SSRIs. Studies of antidepressant prescription redemption have reported rates ranging from 78.6% in the USA[35] to 95.8% in the Netherlands, where 23.7% redeemed only a single prescription.[33] However, even if we conservatively assume that 25% of prescriptions in the UK are not redeemed, the differences observed in our study are much larger than this.

In the UK, the GP is the main source of SSRI prescribing, whereas, in other European countries, a hospital specialist may be more likely to prescribe directly to the patient. In Denmark and the Netherlands, all SSRI prescriptions were captured, with the exception of those issued during a hospital stay. Although prescriptions issued during a hospital stay, prescriptions initiated by a specialist in a hospital outpatient department and private prescriptions were rarely recorded in the UK databases, the numbers were likely to be small. In Italy, prescriptions issued privately or by a specialist which were dispensed at a hospital pharmacy were not captured; based on data from Emilia Romagna for 2010–2011, when these data are included in the database, hospital prescriptions are thought to represent approximately 10% of all SSRI prescribing (A. Puccini, pers. comm.).

In three databases, it was necessary to estimate, for some pregnancies, the duration of pregnancy and the date of the last menstrual period (see Table 1 for details), and this may have resulted in some exposure status misclassification. Our figures are based on women who received a prescription for an SSRI during 11 3-month time periods, and we do not know whether they actually took the product or took it as instructed. In addition, this study did not account for prescriptions issued during one 3-month time period which could have continued to be consumed during the following 3-month time period, and this will have resulted in an underestimation of exposure during some time periods.

This study did not examine the prevalence of depression or the use of other antidepressants. Therefore, the findings do not reflect the full extent to which women are exposed to antidepressants before, during and after pregnancy. It is possible that the higher levels of SSRI prescribing in the UK/Wales could be explained in part by SSRIs making up a larger percentage of all antidepressant prescribing in the UK than in the other regions, but it was not possible to look at this as part of this study. However, current UK prescribing guidelines advise that tricyclic antidepressants are safer than other antidepressants in pregnancy.[36] This study did not examine the indications for prescribing; SSRIs are indicated for a range of conditions in addition to depression, and these may vary between regions. No data were available on the appropriateness of use or efficacy of the SSRIs used.

Comparison with other studies

The percentages of women receiving prescriptions for SSRIs during pregnancy in the areas captured by this study correspond well with other studies for the UK as a whole[37] and for the Netherlands.[8,38] In Denmark, the steady increase in SSRI prescribing during the study period was in line with the increase in SSRI prescribing reported for the general population during a similar study period in Denmark.[39] However, it is not clear whether this trend has continued after 2009. To our knowledge, this is the first study to look at the extent of SSRI prescribing during pregnancy in an Italian population. Prescribing of SSRIs during pregnancy in all European databases was lower than in the USA,[6,7,40,41] where studies have reported percentages of between 5.6%[40] and 10.2%,[6] depending on the years of study and the study setting. The proportions of women receiving prescriptions for SSRIs during the first trimester of pregnancy in the UK were similar to those reported for Australia[9] and Canada.[42]

Interpretation

Other than methodological factors, difference in prescribing may reflect differences in the prevalence of depression, in the severity of depression, in help-seeking behaviour or in prescribing behaviour at national and subnational level. Although the two UK databases both collected data on prescriptions issued, higher levels of SSRI prescribing to women were observed in Wales than in the rest of the UK. This may reflect the higher number of antidepressants prescribed per capita in Wales,[43] and the lower socioeconomic status and per capita income in Wales[44] may also explain in part the discrepancies in prescribing. Regional differences were also observed in Italy, with a lower percentage of females receiving a prescription for an SSRI in Emilia Romagna than in Tuscany; however, this appears to be in line with regional SSRI prescribing differences observed for the general population.[45]

The popularity of paroxetine in Italy and the Netherlands and the absence of a reduction in its prescribing over the study period are surprising, given the number of studies that have demonstrated an increase in the risk of congenital heart defects associated with paroxetine exposure during the early stages of pregnancy.[9,12,46] In the Netherlands, new guidelines on the prescribing of SSRIs during pregnancy were issued in 2012, after the end of our study period; these do not specify a preferred SSRI, but do recommend that, if paroxetine is taken during the periconceptional period, the dose should not exceed 20 mg/day.[47] In Italy, an official safety note was issued by the Italian Medicine Agency in February 2006[48] and, in November 2010, at the end of the study period, a recommendation was issued by the Agency's Paediatric Working Group suggesting that paroxetine should only be used when strictly indicated.[49] UK guidelines recommend that, if a woman taking paroxetine is planning a pregnancy or has an unplanned pregnancy, she should be advised to stop taking the drug and advised that fluoxetine is the SSRI with the lowest known risk during pregnancy,[36] concording with fluoxetine being one of the most popular SSRIs in the UK in our study. The steady increase in the use of citalopram and sertraline during the study period in Denmark and the slight decline in paroxetine correspond to changes to the prescribing guidelines.[50]

When a woman becomes pregnant, the risk–benefit profile of SSRI medication changes, and this is evident from the reduction in SSRI use observed in all European regions during the first trimester of pregnancy, and the further reduction during the second and third trimesters. The efficacy of antidepressant treatment in less than severe depression has been questioned,[51] suggesting a negative benefit–risk balance, except for severe depression. Prescribing guidelines in the UK currently recommend that pregnant women with mild depression should have their medication withdrawn and replaced by self-help or psychological treatments.[36] Further research should investigate whether women with mild depression are being inappropriately prescribed antidepressants during pregnancy, deriving no established benefit, but exposing the fetus to possible risk. Equally important, however, for both mother and baby, is to ensure that depression does not go untreated, that psychological therapies are available where needed and that any discontinuation of SSRI treatment is carried out in a controlled manner. We were not able to establish whether the high rates of discontinuation before and during pregnancy in Europe reflect controlled discontinuation for women who are offered alternative treatments or no longer require treatment, or represent unmet needs and greater levels of depression-related risk among pregnant women.

In Denmark and the Netherlands, a much larger proportion of women using SSRIs before pregnancy continued to receive prescriptions during and after pregnancy compared with the other European regions. This might reflect a more relaxed attitude to SSRI use during pregnancy in Denmark and the Netherlands, but, given the lower percentage of women receiving an SSRI at any time during the study period, it is likely that, in these countries, a larger proportion of women receiving SSRIs have a medical condition sufficiently severe to warrant continuation. The differences observed in postnatal prescribing and the point at which women who had discontinued treatment restarted following delivery may be related in part to differences in the rates of breastfeeding. The percentage of mothers breastfeeding to any extent at 6 weeks post partum has been reported to be approximately 55% in the UK as a whole and 40% in Wales,[52] whereas, in Italy, 49% of mothers are still breastfeeding 3 months after delivery[53] and, in Denmark, 60% are breastfeeding at 4 months post-delivery.[54] The impact of UK guidelines recommending case identification for postnatal depression at 4–6 weeks and 3–4 months post-pregnancy[36] is uncertain, but may have contributed to the higher SSRI prescribing rates observed. Postnatal screening for depression was not routinely carried out in the Netherlands, Italy or Denmark during the study period and, following a policy review in 2011, screening for postnatal depression is no longer recommended in the UK.[55]

Conclusion

The considerably higher levels of SSRI prescribing observed in the UK databases compared with other European databases raises questions about differences in the prevalence and severity of depression and its management in pregnancy across Europe. The variations observed in the type and extent of SSRI prescribing indicate an absence of European consensus on prescribing to pregnant women and women of childbearing age. Further work is required to understand the reasons for the higher levels of SSRI prescribing observed in the UK databases, and the extent to which these reflect medical need and endemic prescribing patterns. Further work is required to better understand the potential adverse fetal and child outcomes following SSRI exposure, and this is the focus of the current EUROmedi-CAT project.[19]

Disclosure of interests

All authors, with the exception of AMNA, AN, AP and RG, received financial support from the European Union for the submitted work under the Seventh Framework Programme (Grant agreement HEALTH-F5-2011-260598). EG, HD, LTWdJ-vdB, AP and AN received grants from EURO-CAT Joint Action (European Commission) for work outside the submitted work. The University of Bath, University of Ulster and University of Groningen received

funding from GlaxoSmithKline for work outside the submitted work, and RAC owns shares in GlaxoSmithKline.

Contribution to authorship

LTWdJ-vdB and HD contributed to the conception of the study. RAC, SJ, AP, EG, AJN and LTWdJ-vdB contributed to the design of the work. Data acquisition and analysis were carried out by AVH, EG and AMNA (Denmark), RG and AP (Tuscany), AP and AJN (Emilia Romagna), HJB and LTWdJ-vdB (the Netherlands), DT, KT and SJ (Wales) and RAC [UK (Clinical Practice Research Datalink, CPRD)]. RAC was the data guarantor. MS contributed to the identification and implications of pregnancy-specific issues in the study. RAC compiled the results for all regions. All authors were involved in the interpretation of the study results, as well as the drafting and revision of the manuscript, and all approved the final version to be published.

Details of ethics approval

Ethical and data access approvals were obtained, where required, for each database from the relevant governance infrastructures. The CPRD Group has obtained ethical approval from a National Research Ethics Service Committee (NRES) for all purely observational research using anonymised CPRD data. Approval was obtained from the CPRD Independent Scientific Advisory Committee (Protocol Number 12_075). The data held by the Health Information Research Unit (HIRU) in the SAIL system are anonymised and have been obtained with the permission of the relevant Caldicott Guardian/Data Protection Officer. Approval was obtained from the HIRU Information Governance Review Panel to use the SAIL system for this research question.

Funding

Financial support for this study was provided by the European Union under the Seventh Framework Programme (grant agreement HEALTH-F5-2011-260598).

Acknowledgements

The authors wish to thank members of the EUROmediCAT Steering Group for their comments on the draft manuscript and, most particularly, Professor Corinne de Vries for her invaluable contribution to the design and interpretation of the study. The authors also thank Dr Saena Arbabzadeh-Bouchez for her comments on earlier drafts of the manuscript. The authors would also like to thank all the data providers who make anonymised data available for research. The work presented in this paper describes anonymised data held in the Secure Anonymised Information Linkage (SAIL) system, which is part of the national e-health records research infrastructure for Wales, and the authors thank David Tucker, Martin Heaven and Leila Pinder for their contribution to the work carried out with SAIL data. This paper also describes data from the Full Feature Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare Products Regulatory Agency. However, the interpretation and conclusions contained in this report are those of the authors alone. The Tuscany Registry of Birth Defects is funded by the 'Direzione Generale Diritti di cittadinanza e Coesione sociale—Regione Toscana'. The authors would like to thank Stefania Biagini and Elisabetta Volpi, UOC Farmaceutica Ospedaliera Fondazione Toscana 'Gabriele Monasterio', Massa (Italy), who provided data on Italian recommendations on medicines use. The Emilia Romagna Registry of Birth Defects is funded by the Emilia Romagna Region Health Authority grant number Delibera 56412/2010.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Percentage of deliveries in which the woman received a prescription for a selective serotonin reuptake inhibitor (SSRI) during the time period of interest, and also received a prescription for (a) an antipsychotic, (b) an anxiolytic and (c) a hypnotic/sedative during the time period of interest. ■

References

1 King M, Nazareth I, Levy G, Walker C, Morris R, Weich S, et al. Prevalence of common mental disorders in general practice attendees across Europe. *Br J Psychiatry* 2008;192:362–7.
2 Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson T. Perinatal depression: a systematic review of prevalence and incidence. *Obstet Gynecol* 2005;106:1071–83.
3 Bennett HA, Einarson A, Taddio A, Koren G, Einarson TR. Prevalence of depression during pregnancy: systematic review. *Obstet Gynecol* 2004;103:698–709.
4 Gruppo di lavoro OsMed. L'uso dei farmaci in Italia. Rapporto nazionale anno 2007 [OsMedWorking Team. The Drug Utilisation in Italy. National Reports 2007]. Rome: Il Pensiero Scientifico Editore; 2008 [www.agenziafarmaco.gov.it/sites/default/files/rapporto_osmed_2007_0.pdf]. Accessed 23 July 2014.
5 Reefhuis J, Rasmussen SA, Friedman JM. Selective serotonin-reuptake inhibitors and persistent pulmonary hypertension of the newborn. *N Engl J Med* 2006;354:2188–90.
6 Cooper WO, Willy ME, Pont SJ, Ray WA. Increasing use of antidepressants in pregnancy. *Am J Obstet Gynecol* 2007;196:544.e541–5.
7 Alwan S, Reefhuis J, Rasmussen SA, Friedman JM, National Birth Defects Prevention Service. Patterns of antidepressant medication use among pregnant women in a United States population. *J Clin Pharmacol* 2011;51:264–70.
8 Bakker MK, Kölling P, Van Den Berg PB, De Walle HEK, De Jong van den Berg LTW. Increase in use of selective serotonin reuptake inhibitors in pregnancy during the last decade, a population-based cohort study from the Netherlands. *J Clin Pharmacol* 2008;65:600–6.

9 Colvin L, Slack-Smith L, Stanley FJ, Bower C. Dispensing patterns and pregnancy outcomes for women dispensed selective serotonin reuptake inhibitors in pregnancy. *Birth Defects Res A Clin Mol Teratol* 2011;91:142–52.

10 Lattimore KA, Donn SM, Kaciroti N, Kemper AR, Neal CR, Vazquez DM. Selective serotonin reuptake inhibitor (SSRI) use during pregnancy and effects on the fetus and newborn: a meta-analysis. *J Perinatol* 2005;25:595–604.

11 Nikfar S, Rahimi R, Hendoiee N, Abdollahi M. Increasing the risk of spontaneous abortion and major malformations in newborns following use of serotonin reuptake inhibitors during pregnancy: a systematic review and updated meta-analysis. *Daru* 2012;20:75.

12 Bakker MK, Kerstjens-Frederikse WS, Buys CH, de Walle HE, de Jong-van den Berg LT. First-trimester use of paroxetine and congenital heart defects: a population-based case–control study. *Birth Defects Res A Clin Mol Teratol* 2010;88:94–100.

13 Chambers CD, Hernandez-Diaz S, Van Marter LJ, Werler MM, Louik C, Jones KL, et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med* 2006;354:579–87.

14 Kieler H, Artama M, Engeland A, Ericsson Ö, Furu K, Gissler M, et al. Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five Nordic countries. *BMJ* 2012;344:d8012.

15 Gentile S. The safety of newer antidepressants in pregnancy and breastfeeding. *Drug Saf* 2005;28:137–52.

16 Toh S, Mitchell AA, Louik C, Werler MM, Chambers CD, Hernandez-Diaz S. Selective serotonin reuptake inhibitor use and risk of gestational hypertension. *Am J Psychiatry* 2009;166:320–8.

17 Cohen L, Altshuler L, Harlow B, Nonacs R, Newport D, Viguera A, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *J Am Med Assoc* 2006;295:499–507.

18 Singh S, Sedgh G, Hussain R. Unintended pregnancy: worldwide levels, trends, and outcomes. *Stud Fam Plann* 2010;41:241–50.

19 EUROmediCAT. Safety of Medication Use in Pregnancy. 2011 [http://euromedicat.eu/]. Accessed 31 July 2014.

20 Dolk H. EUROCAT: 25 years of European surveillance of congenital anomalies. *Arch Dis Child Fetal Neonatal Ed* 2005;90:F355–8.

21 Coloma PM, Trifirò G, Schuemie MJ, Gini R, Herings R, Hippisley-Cox J, et al. Electronic healthcare databases for active drug safety surveillance: is there enough leverage? *Pharmacoepidemiol Drug Saf* 2012;21:611–21.

22 Gagne JJ, Maio V, Berghella V, Louis DZ, Gonnella JS. Prescription drug use during pregnancy: a population-based study in Regione Emilia-Romagna, Italy. *Eur J Clin Pharmacol* 2008;64:1125–32.

23 Ford D, Jones K, Verplancke J-P, Lyons R, John G, Brown G, et al. The SAIL Databank: building a national architecture for e-health research and evaluation. *BMC Health Serv Res* 2009;9:157.

24 Lyons R, Jones K, John G, Brooks C, Verplancke J-P, Ford D, et al. The SAIL databank: linking multiple health and social care datasets. *BMC Med Inform Decis Mak* 2009;9:3.

25 Wood L, Martinez C. The General Practice Research Database: role in pharmacovigilance. *Drug Saf* 2004;27:871–81.

26 Thygesen LC, Daasnes C, Thaulow I, Brønnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. *Scand J Public Health* 2011;39(7 Suppl):12–16.

27 Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;39(7 Suppl):30–3.

28 Wallach Kildemoes H, Toft Sørensen H, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011;39(7 Suppl):38–41.

29 Visser ST, Schuiling-Veninga CCM, Bos JHJ, de Jong-van den Berg LTW, Postma MJ. The population-based prescription database IADB.nl: its development, usefulness in outcomes research and challenges. *Expert Rev Pharmacoecon Outcomes Res* 2013;13:285–92.

30 Charlton RA, Neville AJ, Jordan S, Pierini A, Damase-Michel C, Klungsøyr K, et al. Healthcare databases in Europe for studying medicine use and safety during pregnancy. *Pharmacoepidemiol Drug Saf* 2014;23:586–94.

31 van Gelder MHJ, Rooij ILM, Walle HK, Roeleveld N, Bakker M. Maternal recall of prescription medication use during pregnancy using a paper-based questionnaire. *Drug Saf* 2013;36:43–54.

32 Jordan S, Watkins A, Storey M, Allen SJ, Brooks CJ, Garaiova I, et al. Volunteer bias in recruitment, retention, and blood sample donation in a randomised controlled trial involving mothers and their children at six months and two years: a longitudinal analysis. *PLoS One* 2013;8:e67912.

33 van Geffen ECG, Gardarsdottir H, van Hulten R, van Dijk L, Egberts ACG, Heerdink ER. Initiation of antidepressant therapy: do patients follow the GP's prescription? *Br J Gen Pract* 2009;59:81–7.

34 Beardon PH, McGilchrist MM, McKendrick AD, McDevitt DG, MacDonald TM. Primary non-compliance with prescribed medication in primary care. *BMJ* 1993;307:846–8.

35 Fischer MA, Stedman MR, Lii J, Vogeli C, Shrank WH, Brookhart A, et al. Primary medication non-adherence: analysis of 195,930 electronic prescriptions. *J Gen Intern Med* 2010;25:284–90.

36 National Institute for Health and Clinical Excellence. Antenatal and postnatal mental health. Clinical management and service guidance. 2007 [www.nice.org.uk/guidance/cg45/resources/guidance-antenatal-and-postnatal-mental-health-pdf]. Accessed 18 August 2014.

37 Petersen I, Gilbert RE, Evans SJ, Man SL, Nazareth I. Pregnancy as a major determinant for discontinuation of antidepressants: an analysis of data from The Health Improvement Network. *J Clin Psychiatry* 2011;72:979–85.

38 Ververs T, Kaasenbrood H, Visser G, Schobben F, Jong-van den Berg L, Egberts T. Prevalence and patterns of antidepressant drug use during pregnancy. *Eur J Clin Pharmacol* 2006;62:863–70.

39 Engelbrecht AST. *Forbruget af Antidepressiva 2001–2011*. Dataleverancer og Lægemiddelstatistik Sektor for National Sundhedsdokumentation og Forskning. Copenhagen: Statens Serum Institute, 2012. 21 May 2013.

40 Andrade SE, Raebel MA, Brown J, Lane K, Livingston J, Boudreau D, et al. Use of antidepressant medications during pregnancy: a multisite study. *Am J Obstet Gynecol* 2008;198:194.e191–5.

41 Huybrechts KF, Palmsten K, Mogun H, Kowal M, Avorn J, Setoguchi-Iwata S, et al. National trends in antidepressant medication treatment among publicly insured pregnant women. *Gen Hosp Psychiatry* 2013;35:265–71.

42 Ramos É, Oraichi D, Rey É, Blais L, Bérard A. Prevalence and predictors of antidepressant use in a cohort of pregnant women. *BJOG* 2007;114:1055–64.

43 Heaney P. Antidepressant prescriptions up amid therapy delays. 2012 [www.bbc.co.uk/news/uk-wales-19289669]. Accessed 12 November 2013.

44 Office for National Statistics. Regional Gross Disposable Household Income (GDHI) 2011. 2013 [www.ons.gov.uk/ons/dcp171778_307651.pdf]. Accessed 1 October 2013.

45 Damiani G, Federico B, Silvestrini G, Bianchi C, Anselmi A, Iodice L, et al. Impact of regional copayment policy on selective serotonin reuptake inhibitor (SSRI) consumption and expenditure in Italy. *Eur J Clin Pharmacol* 2013;69:957–63.

46 Wurst KE, Poole C, Ephross SA, Olshan AF. First trimester paroxetine use and the prevalence of congenital, specifically cardiac, defects: a meta-analysis of epidemiological studies. *Birth Defects Res A Clin Mol Teratol* 2010;88:159–70.

47 Nederlandse Vereniging voor obstetrie en gynaecologie (NVOG). Richtlijn. SSRI-gebruik in de zwangerschap en tijdens lactatie. 2012 [www.nvog-documenten.nl]. Accessed 5 May 2013.

48 Agenzia Italiana del Farmaco AIFA. Nota informativa importante concordata con le autorità regolatorie Europee e l'Agenzia Italiana del Farmaco (AIFA). 2006 [www.agenziafarmaco.gov.it/sites/default/files/111.86876.11401890146983587.pdf]. Accessed 30 September 2013.

49 Agenzia Italiana del Farmaco AIFA. Raccomandazioni del Working Group Pediatrico dell'AIFA in relazione all'eposizione *in utero* di antidepressivi. 2010 [www.agenziafarmaco.gov.it/sites/default/files/paroxetina_raccomandazione_wgp_23112010.pdf]. Accessed 30 September 2013.

50 Videbech P, Christensen KS, Hansen PEB. Antidepressiv behandling af gravide 2013. [http://pro.medicin.dk/Sygdomme/Sygdom/318339]. Accessed 25 August 2014.

51 Fournier JC, DeRubeis RJ, Hollon SD, Dimidjian S, Amsterdam JD, Shelton RC, et al. Antidepressant drug effects and depression severity: a patient-level meta-analysis. *J Am Med Assoc* 2010;303:47–53.

52 McAndrew F, Thompson J, Fellows L, Large A, Speed M, Renfrew M. The Infant Feeding Survey 2010. NHS Information Centre for Health and Social Care, Office of National Statistics. 2012 [http://data.gov.uk/dataset/infant-feeding-survey-2010]. Accessed 22 June 2013.

53 Lauria L, Spinelli A, Lamberti A, Buoncritiano M, Bucciarelli M, Andreozzi S, et al. Breastfeeding: prevalences, duration and associated factors from two Italian surveys – 2008 and 2011. Not Ist Super Sanità 2012;25:i–iii. [www.epicentro.iss.it/ben/2012/november/2011.asp]. Accessed 30 January 2014.

54 Busck-Rasmussen M, Fredsted Villadsen S, Nyboe Norsker F, Mortensen L, Nybo Andersen A. Breastfeeding practices in relation to country of origin among women living in Denmark: a population-based study. *Matern Child Health J* 2014;18:2479–2488.

55 UK National Screening Committee. Postnatal depression screening policy position statement. 2011 [www.screening.nhs.uk/policydb_download.php?doc=189]. Accessed 1 October 2013.